This Month in Genetics

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The Sound of Silence

The genetic code is degenerate, meaning that more than one codon can specify an amino acid. When a mutation alters a codon but not the amino acid it encodes, we call it a synonymous mutation and assume it has no effect. Recent evidence suggests that we may have to rethink the idea that these changes are silent. The evidence comes from comparisons of β- and γ-actin, which are 98% identical at the amino acid level but have strikingly different localizations and functions in cells. β-actin was known to be arginylated at its N terminus, and a lack of this posttranslational modification alters its localization, suggesting that it could be at least partially responsible for the divergence in function between the two actins. When Zhang et al. looked closely at γ-actin, however, they found that it is also arginylated but that this form of γ-actin is rapidly degraded by the proteasome. Why? The difference turns out to be due to differences in codon usage in the first stretch of the two genes. The codons used for γ-actin are predicted to slow the rate of translation of the protein, relative to those that encode β-actin. This appears to allow time before the protein folds for a normally internal lysine in the nascent γ-actin protein to be ubiquitinated, targeting it for degradation. Indeed, when the authors exchanged β-actin codons with those used for γ-actin while completely maintaining the β-actin amino acid sequence, β-actin was destabilized. In the converse experiment, γ-actin that used β-actin codons was stabilized. If protein function can be determined at the nucleotide level, we still have a lot to learn about the complexity of the genetic code, and we may be ignoring relevant synonymous changes.

Zhang et al. Science 329, 1534–1537. 10.1126/science.1191701.

The Difference between No Protein and Some

Several mutations in the gene encoding presenilin-1 have been reported in early-onset autosomal-dominant Alzheimer disease (AD). All of these mutations have so far been missense or in-frame changes to the gene. A recent paper reports a surprising allelic disorder with this early onset form of AD: acne inversa. This chronic and painful inflammatory skin disease mainly involves areas of skin with apocrine glands, such as the armpits and groin area and can cause extensive scarring. Presenilin is the catalytic subunit of the γ-secretase, which cleaves such proteins as amyloid precursor protein and Notch. It works in complex with three cofactor subunits: PEN2, NCT, and APH1. Of six families with acne inversa who were examined in this study, all had mutations in components of this protease. Affected individuals from two families had frameshift mutations in the gene encoding PEN2, whereas the other four families appeared to exhibit digenic inheritance; each affected individual carried frameshift or nonsense mutations in each of two genes, those encoding presenilin and NCT. This suggests that complete loss of function of part of this complex causes an inflammatory disease of hair follicles and that a missense change causes a neurodegenerative disorder. This intriguing finding suggests that we have a lot more to discover about the work of γ-secretase. Furthermore, it suggests that the multiple presenilin knockout animal models might not capture the relevant disease process for AD.

Wang et al. Science Express. Published online October 7, 2010. 10.1126/science/1196284.

Too Many Qs, Not Enough Answers (But Getting There)

Although polyglutamine (polyQ) is the common link to several neurodegenerative diseases, there must be more to the toxic mechanism than just the polyQ, because each disease is distinct and involves different neurons. Data suggest that the protein context in which the polyQ resides is critical to the outcome, but whether and how the native function of these proteins influences the disease pathogenesis is an open question. The gene that is involved in spinobulbar muscular atrophy (SBMA) encodes the androgen receptor (AR), one of the few polyQ-associated proteins that have a well understood function. This led Nedelsky et al. to use a *Drosophila* model to zero in on the relevance of specific steps in AR function to polyQ-mediated neurodegeneration. Through the mutation of various domains of AR, they demonstrate that normal functions of AR, including translocation to the nucleus, DNA binding, and interaction with other proteins, are required for polyQ toxicity in their model. As a control in their experiments, the authors used AR with a wild-type-length polyQ tract and found that, unexpectedly, high levels of expression of this construct caused neurodegeneration. Putting this together with their other results, they surmise that neurodegeneration in SBMA may be at least partially the result of enhancement of native functions or interactions of the AR.

Nedelsky et al. Neuron 67, 936–952. 10.1016/j.neuron.2010.08.034.

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Here's to Homogeneity

Although the main way that we lump cancers into groups is based on the tissue that is affected, there is clearly heterogeneity in these groups in terms of pathology and outcomes. Splitting these groups into more homogeneous subsets on the basis of pathology and, increasingly, the mutational composition of the tumors is aimed at making better predictions of outcome and developing more targeted treatments for each subset. Recent work by Antoniou et al. suggests that this splitting of groups could also improve the power to detect genetic susceptibility alleles for cancer. Their research was instigated by the finding that few of the known breast cancer susceptibility alleles modify risk of breast cancer in women with *BRCA1* mutations and thus do not contribute to the incomplete penetrance of the *BRCA1* mutations. This led them to conduct a genome-wide association study in *BRCA1* mutation carriers, comparing those who had invasive breast cancer by age 40 with those who had not been diagnosed with breast cancer. They identified a region of chromosome 19p13 that influences the risk of breast cancer, particularly estrogen receptor negative disease, in women with *BRCA1* mutations, and they went on to show that it is more broadly associated with risk of estrogen receptor negative breast cancer, a type of cancer that makes up less than one-quarter of breast cancers in women of European ancestry. As outlined in the accompanying News & Views by Kraft and Haiman, failure to take into account tumor subtype vastly reduces the power to detect an association signal that is specific to one subtype, such as the one at chromsome 19p13. Beyond the potential for additional risk information for carriers of *BRCA1* mutations, this locus could lead to greater understanding of the development of estrogen receptor negative breast cancer, which currently has a worse prognosis than the more common estrogen receptor positive disease.

Antoniou et al. Nature Genetics 42, 885–892. 10.1038/ng.669.

Breathing Easier with Rett Syndrome

Breathing irregularities, including episodic apnea, are a common feature of the neurological disorder Rett syndrome and are recapitulated in Mecp2-deficient mice. A recent study by Abdala et al. shows that apnea in the mouse model is characterized by excessive excitatory activity in expiratory cranial and spinal nerves. On the basis of this fact, together with the fact that these mice have deficits in GABA synaptic inhibition, the authors decided to test whether augmenting GABA might improve the breathing problems associated with Mecp2 deficiency. Indeed, this treatment decreases the incidence of apnea in heterozygous knockout female mice. The results are even better when GABA reuptake inhibitors are given in combination with a serotonin agonist; the combination treatment reduces the incidence of apnea to wild-type levels and corrects the breathing irregularities. This work suggests the possibility that drug treatment could be used to moderate breathing irregularities in girls with Rett syndrome because the underlying respiratory control network is intact.

Abdala et al. PNAS 107, 18208–18213. 10.1073/pnas.1012104107.

This Month in Our Sister Journals

Phenotype to Genotype and Back Again?

More and more copy-number variations (CNV) in the human genome are being named culprits in neurodevelopmental disorders, including the autism spectrum disorders (ASDs). Sometimes, though, the use of a referring diagnosis as the sole phenotypic feature of interest limits our understanding of the potential phenotypic consequences of a CNV. To go beyond this one-dimensional view, Rosenfeld et al. sorted twice through their large collection of samples that were tested for CNV, using microarray-based comparative genomic hybridization. The first time, they analyzed only samples from individuals who were referred for testing for ASD, and they found a potentially causative abnormality in 7.7% of samples overall. These included 41 autosomal regions that do not have a well described association with ASD. The second time that they sorted through their samples, they looked for individuals without an ASD referral who had overlapping CNV with these 41 regions, and they found that only 19% of them had autistic features or an ASD diagnosis. Together with the fact that some of these CNVs overlap with those previously identified in patients with other neurodevelopmental disorders, including schizophrenia and attention deficit hyperactivity disorder, this analysis could suggest that the CNVs are associated with a range of neurodevelopmental phenotypes, albeit a suggestion that needs to be more clearly elucidated. Because many of the CNVs in this study are inherited from presumably normal parents, the authors presume that, even with a contributing CNV, the inheritance of these phenotypes may be more akin to a complex trait than we might have hoped, making predictions of phenotype based on the presence of one of these CNVs tenuous.

Rosenfeld et al. Genetics in Medicine. Published online August 30, 2010. 10.1097/GIM.0b013e3181f0c5f3.

Go Ahead and Have Another Cup

Ah, coffee! Besides its aromatic appeal, epidemiological studies suggest that it reduces the risk of Parkinson disease and Alzheimer disease (AD). The question is: How? In a recent paper in *Genetics*, Dostal et al. use *C. elegans* as

a model system to figure out how coffee might be neuroprotective. In their worm model, inducible expression of human $A\beta_{42}$, a peptide that plays a key role in the development of AD, leads to rapid paralysis. The paralysis is rescued if the worms are grown in agar that contains a coffee extract. Although full-octane coffee works better in this assay than does decaf, the fact that pure caffeine is not protective to the worms suggests that it isn't the major source of the protective effect. Coffee extracts confer protection by inducing the *skn-1* detoxification pathway, an effect that can be blocked through knockdown or mutation of *skn-1*. The functional equivalent of Skn-1 in mammals is Nrf2, which is neuroprotective in a variety of mammalian neurodegeneration models and believed to be induced by coffee, thereby linking this pathway back to the reduced risk of AD in coffee drinkers. Understanding this mechanistic link to the epidemiological data means that the dietary modulation of this neuroprotective pathway can be further explored. So go ahead and have that second cup; it might be good for you.

Dostal et al. Genetics. Published online August 30, 2010. 10.1534/genetics.110.120436.